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EDITORIAL COMMENT

Moore's Law: Apples and Oranges*

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In 1965, Gordon Moore, then Fairchild Semiconductor's director of Research and Development, attempted to predict the continued development of integrated electronics by a principle now known as "Moore's law" in the semiconductor industry and modern computing. In essence, it describes the fact that the number of transistors on an integrated circuit has been doubling approximately every 2 years, making devices more efficient, more powerful, and better able to do "complex procedures" than ever. An analogous principle could be construed to exist in the field of interventional cardiology, where every 18 months or so a new generation of devices is introduced into the marketplace that are designed to improve the outcomes of complex procedures in increasingly complex patients. Interventional cardiology has first-generation drug-eluting stents (DES), which are not even manufactured anymore, and subsequent second-, third-, and now even fourth-generation DES. The question remains, despite the fact that Moore's law as a driving principle in integrated electronics has resulted in dramatic improvements in complex procedures, whether new generations of DES translate to similar improvements in complex procedures in interventional cardiology.

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The patient-level pooled analysis by Piccolo et al. (1), in this issue of *JACC: Cardiovascular Interventions*, of 6,081 patients comparing the effectiveness and safety of new-generation versus early generation DES is focused on evaluating technological improvements. It is important for several reasons. Despite the fact that trials and randomized studies of percutaneous coronary intervention (PCI) with DES versus coronary artery bypass graft (CABG) for the treatment of multivessel disease have been concordant in finding that composite endpoints of death, stroke, and target lesion revascularization are still better with coronary bypass graft surgery (2–8), the iterative science/art of interventional cardiology continues to work on technological improvements that could potentially narrow the gap and allow PCI to be considered as equivalent in the setting of complex multivessel disease (9). Because randomized trials of DES versus CABG were typically carried out with first-generation stents, as technology has improved, so might the longer-term efficacy and safety results. In the Piccolo et al. (1) analysis, the individual patient-level data from 4 recent randomized clinical trials conducted between 2004 and 2013 with the exclusive use of DES (SIRTAX [Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization], LEADERS [Limus Eluted From a Durable Versus Erodible Stent Coating], RESOLUTE All Comers [Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention], and BIOSCIENCE [Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization]) were analyzed. All of the trials included both stable and acute coronary syndrome patients; the first-generation DES stents used were the first 2 DES approved in the United States (sirolimus: Cypher or Cypher Select, Cordis, Miami Lakes, Florida; and paclitaxel: Taxus, Boston Scientific, Natick, Massachusetts). The newer generation stents include everolimus, zotarolimus, and biodegradable polymers, biolimus, and sirolimus. The primary device-oriented clinical endpoint was the composite of cardiac death, nonfatal myocardial infarction, or ischemia-driven target lesion revascularization (TLR). Effectiveness and safety endpoints were TLR and definite stent thrombosis.

In the overall population, Moore's law of improved performance by technologic improvements was validated. At 2 years, the primary endpoint in an adjusted analysis was significantly improved with

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new-generation DES (hazard ratio [HR]: 0.75, 95% confidence interval [CI]: 0.63 to 0.89, p = 0.001). Similarly, cardiac death (HR: 0.60, 95% CI: 0.42 to 0.85, p = 0.004), clinically indicated TLR (HR: 0.56, 95% CI: 0.44 to 0.70, p < 0.001), target vessel revascularization (HR: 0.61, 95% CI: 0.49 to 0.75, p < 0.001), and definite stent thrombosis (HR: 0.40, 95% CI: 0.25 to 0.65, p < 0.001) were all significantly improved (see Figures 3A, 3B, 4A, and 5 in Piccolo et al. [1]). Accordingly, the investigators conclude that "new generation DES improved clinical outcomes compared with earlier generation DES."

The rest of the story is different and deals with apples and oranges, although both are fruits, are quite different. This relates to a second primary focus of the study—to compare the outcome of PCI depending on the complexity of coronary artery disease. Unfortunately, apples and oranges are mixed here. The investigators relate their analysis to the pivotal SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) trial and the SYNTAX score based upon the complexity of coronary artery disease. A crucial analysis in the original SYNTAX publication was the use of tertiles of complexity with a low score ≤22, an intermediate score of 23 to 32, and a high score ≥33 (2).

In the final 5-year analysis of the SYNTAX trial, there were important differences in outcomes based upon the tertile SYNTAX score (10). In patients in the lowest tertile (score 0 to 22), there was no significant difference in outcome between CABG and PCI; there was only a trend in difference in revascularization (p = 0.056). This occurred even despite the use of first-generation DES. There was, however, a significant difference between CABG and PCI in patients in the middle and upper tertiles with CABG being significantly better. Unfortunately, the current paper by Piccolo et al. (1) confuses us in some ways because it groups patients apparently by design into only low or high complexity using the median score ≤11 or ≥11. In this analysis, in the "high CAD complexity group" some patients may have been considered in the lowest tertile in the SYNTAX trial making any potential comparisons difficult. Although according to the statistical analysis plan, it appears that this grouping into "low and high complexity" was by design, it would have been easier to interpret the findings if the SYNTAX tertile grouping had been used. It would have been particularly valuable to know the performance of a new-generation DES in the highest risk tertile of the patients using the cutoff of ≥33. In this most complex group of patients, CABG has been found to be substantially superior. Given that this is a large group of multivessel disease patients, attempts at expanding PCI with new technology should be at least assessed in this group.

Irrespective of the issues of apples (SYNTAX score ≤11 vs. ≥11) and oranges (STYNTAX score ≤22, 22 to 32 and ≥33), this study adds important information to the published data. Patients with a higher SYNTAX score >11 receiving a new-generation DES had significantly improved primary major adverse cardiac event rates (HR: 0.68, 95% CI: 0.54 to 0.85, p = 0.001) compared with the patients with less complex disease in whom the difference was not significant. Similarly, cardiac death was significantly less (p < 0.001) in patients with SYNTAX score >11 receiving a new-generation DES but was not significantly different in patients with less complex disease. Other endpoints included clinically indicated TLR, target vessel revascularization, and stent thrombosis were all significantly less in the "high complexity" with newer-generation DES but were not different in patients with less complex disease. The investigators could have concluded from this part of the paper that "new generation DES improved clinical outcomes compared with early generation DES with clinically significant greater safety and effectiveness only in patients with SYNTAX score >11."

Where then do we, as individual cardiologists and cardiovascular surgeons, stand with this new robust analysis of data from 4 recent large trials? We can say:

1. Moore's law in integrated electronics, where important advances occur with each new generation, is also true in interventional cardiology, and new DES stents perform better in terms of safety and effectiveness than older versions do.
2. In patients with clinical moderate disease, the impact of these new stents is more important as the disease becomes more complex.
3. In patients with the most complex disease (SYNTAX score >33) we do not know the impact of these new stents, and for now the results of the randomized clinical trials on CABG versus PCI in these most complex patients remains untested. In the meantime, we can look forward to the results of the completely enrolled Excel Clinical Trial NCT01205776 of everolimus eluting stents in patients with left main disease and a SYNTAX score <33 for validation of the progress that this meta-analysis appears to demonstrate.

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